Fish Consumption and Cognitive Decline With Age in a Large Community Study

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Background: Dietary intake of fish and the ω-3 fatty acids have been associated with lower risk of Alzheimer disease and stroke.

Objective: To examine whether intakes of fish and the ω-3 fatty acids protect against age-related cognitive decline.

Design: Prospective cohort study.

Setting: Geographically defined Chicago, Ill, community.

Participants: Residents, 65 years and older, who participated in the Chicago Health and Aging Project.

Main Outcome Measure: Change in a global cognitive score estimated from mixed models. The global score was computed by summing scores of 4 standardized tests. In-home cognitive assessments were performed 3 times over 6 years of follow-up.

Results: Cognitive scores declined on average at a rate of 0.04 standardized units per year (SU/y). Fish intake was associated with a slower rate of cognitive decline in mixed models adjusted for age, sex, race, education, cognitive activity, physical activity, alcohol consumption, and total energy intake. Compared with a decline rate in score of −0.100 SU/y among persons who consumed fish less than weekly, the rate was 10% slower (−0.090 SU/y) among persons who consumed 1 fish meal per week and 13% slower (−0.088 SU/y) among persons who consumed 2 or more fish meals per week. The fish association was not accounted for by cardiovascular-related conditions or fruit and vegetable consumption but was modified after adjustment for intakes of saturated, polyunsaturated, and trans fats. There was little evidence that the ω-3 polyunsaturated fatty acids were associated with cognitive change.

Conclusions: Fish consumption may be associated with slower cognitive decline with age. Further study is needed to determine whether fat composition is the relevant dietary constituent.

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IN PREVIOUS STUDIES, FISH CONSUMPtion was associated with lower risk of incident dementia[1-3] and stroke.[4-7] Fish is a direct source of ω-3 fatty acids, a class of polyunsaturated fat that has been associated with lower risk of Alzheimer disease[3] and cognitive decline[8] in 2 prospective studies. Dietary intakes of the ω-3 fatty acids, and especially docosahexaenoic acid (DHA), are essential for neurocognitive development and normal brain functioning.[9,10] Recent animal models have demonstrated that dietary DHA is important for brain neural reserve and memory performance in aged mice.[11-14] In the current study, we examined whether dietary consumption of fish and the ω-3 fatty acids were associated with age-related cognitive decline among a large population of older adults.

METHODS

STUDY POPULATION

Subjects were participants in the Chicago Health and Aging Project (CHAP),[15] an ongoing study of 6158 residents 65 years and older of a geographically defined community (78.9% of eligible residents) that is 62% black and 38% white. Baseline in-home interviews that included cognitive testing were conducted from 1993 to 1997 and repeated in 2 follow-up interviews every 3 years. Study participants completed a self-administered food frequency questionnaire (FFQ) a median of 1.2 years from the baseline. A total of 4390 study participants had at least 2 cognitive assessments (1298 died before follow-up). Of these, we eliminated 213 persons who had an invalid FFQ and 455 persons who completed the FFQ more than 2.5 years after baseline, leaving 3718 persons for the analysis of cognitive change.

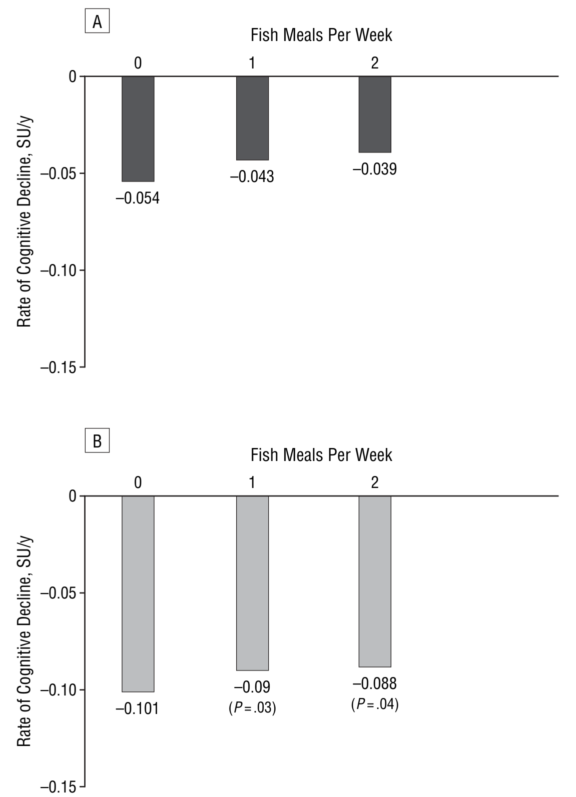

Figure. Annual rate of change in cognitive score (standardized units per year [SU/y]) by number of fish meals per week based on mixed models. A, Basic adjusted model included terms for age (years), age^2, energy intake (kilocalories per day, linear, squared, and cubic terms), sex, race, education (years, linear and squared terms), education × race, sex × age, time, 1 fish meal per week, 2 fish meals or more per week, and time interactions with each of age, energy intake, education, sex, race, education × race, 1 fish meal per week, and 2 or more fish meals per week. B, Multiple-adjusted model included terms from the basic adjusted model plus cognitive activity, physical activity, alcohol consumption (grams per day, linear and squared terms), and time interactions with each term.

The institutional review board of Rush University Medical Center, Chicago, Ill, approved the study, and all participants gave written informed consent.

DIETARY ASSESSMENT

Diet was assessed by a modified Harvard FFQ[16,17] that asked about usual frequency of intake in the past year of 139 different foods. The FFQ included 4 seafood items (tuna fish sandwich, fish sticks/fish cakes/fish sandwich, fresh fish as a main dish, and shrimp/lobster/crab). Weekly consumption of fish was computed by summing the responses to the 3 fish items. Daily intakes of specific nutrients were obtained by multiplying the nutrient content of individual food items by the frequency of consumption and summing over all items. Total ω-3 fatty acid intake included α-linolenic acid (18:3ω-3), eicosapentaenoic acid (EPA) (20:5ω-3), docosapentaenoic acid (22:5ω-3), and DHA (22:6ω-3). Polyunsaturated fat included intakes of total ω-3 fatty acids, linoleic acid (18:2ω-6), and arachidonic acid (20:4ω-6). Nutrient intakes were energy-adjusted by the regression residual method.[18]

Spearman rank correlation coefficients for 1-year reproducibility of nutrient intakes among 133 CHAP participants were: $r = 0.55$ for total ω-3 fatty acids, $r = 0.58$ for DHA, and $r = 0.44$ for EPA (all $P < .001$). The correlation was $r = 0.33$ ($P = .01$) between plasma and FFQ levels of the marine ω-3 fatty acids measured in 56 participants.

COGNITIVE TESTING

Cognition was measured by 4 tests: the East Boston Tests of Immediate and Delayed Recall,[19,20] the Mini-Mental State Examination,[21] and the Symbol Digit Modalities Test.[22] Standardized scores were computed for each test using the baseline population mean and standard deviation (*z* scores), and then the 4 tests were averaged into a single global measure. The global measure was more normally distributed than the individual cognitive tests and had reduced problems of measurement error.

COVARIATES

Nondietary variables were collected at participants' baseline interview and included demographic variables, cognitive activity (average frequency of participation in 7 activities[23]), physical activity (hours per week of 9 activities), alcohol consumption (grams per day of beer, wine, and liquor), number of depressive symptoms,[24] heart disease (self-reported history of myocardial infarction or digitalis use), hypertension (self-reported history or measured blood pressure ≥160 mm Hg systolic or ≥95 mm Hg diastolic), stroke history (self-report), and diabetes mellitus (self-report or antidiabetic medication use).

STATISTICAL ANALYSIS

Change in cognitive function over 6 years was examined using random coefficients mixed models[25] in SAS (SAS Institute Inc, Cary, NC). The mixed model simultaneously estimates average overall level of cognitive score and rate of change while also accounting for within-person variation in these estimates.

Fish intake was modeled with indicator variables for weekly frequency of consumption. Nutrient intakes of total and individual ω-3 fatty acids were modeled in quartiles. The lowest intake levels were the referent categories. Before modeling the dietary exposure variables, we first determined the best model of confounders, including nonlinear and interaction terms. Tests for effect modification were performed in basic adjusted models (**Figure**) that included interaction terms between fish consumption (at least weekly vs less often) and the potential effect modifier, with $P \leq .05$ level of statistical significance.

RESULTS

Fish consumption was low to moderate, with 21.0% of participants eating 2 or more fish meals per week; 36.3%, 1 fish meal per week; and 42.6%, less than 1 (**Table 1**). Fish consumers were more likely to be of black race and to have a cardiovascular-related health condition. They also tended to drink less alcohol than the nonconsumers, but educational level was comparable across the intake groups.

The mean cognitive score at baseline was 0.18 standardized units (SU) (range, −3.5 to 1.6 SU), and the overall rate of change was a decline of 0.04 SU per year (SU/y). Cognitive decline was slower among persons who consumed fish at least weekly. In the model adjusted for age, sex, race, education, and total energy intake, scores declined by 0.054 SU/y among infrequent consumers, 0.043 SU/y among weekly consumers, and by 0.039 SU/y among more than weekly consumers (Figure A). When

Table 1. Baseline Characteristics by Fish Consumption Among 3718 Persons, Chicago Health and Aging Project, 1993-1997*

Characteristic	Fish Meals/wk 0	1	≥2
No. of participants	1585	1351	782
Age, mean, y	74.6	74.2	73.9
Men, %	39.6	36.7	36.8
Black, %	54.9	61.2	70.4
Education, mean, y	12.2	12.3	12.1
Total energy intake, mean, kcal/d	1568	1768	2065
Cognitive activities score, mean	3.2	3.2	3.2
Physical activities, mean, h/wk	3.4	3.7	3.9
No. of depressive symptoms, mean	1.5	1.6	1.6
Alcohol consumption, mean, g/d	4.8	3.8	3.6
Myocardial infarction, %	16.5	16.4	18.5
Stroke, %	7.5	8.9	8.2
Diabetes mellitus, %	15.0	18.2	19.8
Hypertension, %	52.4	57.1	57.3
Fats			
Saturated, mean, g/d	18.6	18.4	16.7
Transunsaturated, mean, g/d	3.5	3.5	3.1
Polyunsaturated, mean, g/d	10.8	11.8	11.3
Vegetable consumption, mean, servings/d	2.0	2.3	2.9
Fruit consumption, mean, servings/d	2.0	2.1	2.6

SI conversion factor: To convert kilocalories to kilojoules, multiply by 4.2.
*All characteristics are age standardized.

we further adjusted for cognitive activity, physical activity, and alcohol consumption, the differences in rates compared with nonconsumers were 0.011 SU/y ($P = .03$) for weekly consumers and 0.013 SU/y ($P = .04$) for consumers of 2 or more fish meals per week, annual rate reductions of 10% and 13%, respectively (Figure B).

There was little evidence of association between intakes of the ω-3 fatty acids and cognitive change in multiple-adjusted models that adjusted for dietary intakes of vitamin E and niacin, total vitamin C, and saturated and trans fats (**Table 2**). When we reanalyzed the data after eliminating persons who reported eating more fish now than they did 10 years ago, the rate differences for higher levels of ω-3 fatty acid intake increased, but only the rate differences for the fourth and fifth quintiles of α-linolenic acid intake approached statistical significance (Table 2).

We examined the extent to which the observed fish association may be due to its protective effects on cardiovascular-related conditions by adding terms to the multiple-adjusted model for history of stroke, myocardial infarction, hypertension, and diabetes mellitus. However, the rate differences for weekly and more than weekly fish consumption were not materially different ($\beta = 0.012$; $P = .02$ and $\beta = 0.013$; $P = .03$, respectively).

To examine whether the fish association may be due to dietary consumption patterns, we added terms for vegetable and fruit intakes to the multiple-adjusted model, but the rate differences did not change appreciably ($\beta = 0.011$; $P = .03$ and $\beta = 0.012$; $P = .05$ for 1 and 2 or more fish meals per week, respectively). However, adjustment for intakes of saturated (grams per day), polyunsaturated (grams per day), and trans (grams per day) fats modified

Table 2. Nutrient- and Multiple-Adjusted Differences in Rate of Change in Cognitive Score Over 6 Years by ω-3 Fatty Acid Intake Among 3718 CHAP Participants and 2679 of the Long-term Fish Consumers, 1993-2002*

Model	Quartile of Intake 1	2	3	4	*P* Value for Trend
Total ω-3 fatty acids					
Mean g/d	0.84	1.07	1.24	1.59	
Total cohort					
β	0	0.004	0.011	0.003	
P value	Referent	.52	.11	.74	.78
Long-term fish consumers					
β	0	0.009	0.018	0.007	
P value	Referent	.27	.03	.40	.48
Docosahexaenoic acid					
Mean g/d	0.03	0.05	0.08	0.15	
Total cohort					
β	0	0.003	0.009	0.004	
P value	Referent	.60	.16	.53	.63
Long-term fish consumers					
β	0	0.005	0.15	0.13	
P value	Referent	.50	.06	.15	.14
Eicosapentaenoic acid					
Mean g/d	0.01	0.02	0.03	0.07	
Total cohort					
β	0	0.006	0.008	0.001	
P value	Referent	.33	.24	.91	.88
Long-term fish consumers					
β	0	0.012	0.009	0.010	
P value	Referent	.08	.23	.21	.34
α-Linolenic acid					
Mean g/d	0.75	0.97	1.14	1.45	
Total cohort					
β	0	0.007	0.015	0.009	
P value	Referent	.29	.03	.22	.23
Long-term fish consumers					
β	0	0.010	0.020	0.017	
P value	Referent	.21	.02	.07	.07

Abbreviation: CHAP, Chicago Health and Aging Project.
*Models included terms from the multiple-adjusted model described in the Figure plus food intake of vitamin E (milligrams per day), total vitamin C (milligrams per day), food intake of niacin (milligrams per day), saturated fat (grams per day), trans fat (grams per day), and quartiles of ω-3 fatty acid intake.

the rate differences for both weekly ($\beta = 0.010$; $P = .05$) and more than weekly fish consumers ($\beta = 0.010$; $P = .10$).

The estimated fish effects did not differ by age, sex, race, or education. The multiple-adjusted rate differences did not change appreciably when we eliminated persons in the lowest 10% of baseline cognitive scores ($\beta = 0.012$; $P = .02$ for 1 fish meal per week; $\beta = 0.013$; $P = .04$ for 2 or more fish meals per week).

COMMENT

Dietary intake of fish was inversely associated with cognitive decline over 6 years in this older, biracial community study. The rate of decline was reduced by 10% to 13% per year among persons who consumed 1 or more fish meals per week compared with those with less than weekly consumption. The rate reduction is the equivalent of being 3 to 4 years younger in age. There were no consistent associations with the ω-3 fatty acids, although the effect estimates were in the direction of slower decline.

Cognitive decline is common among older people and is very much associated with advancing age. Our data offer no insight as to whether this cognitive decline is pathological or the result of a normal aging process. Nonetheless, data from the United States and other countries indicate that it is a widespread and increasing public health problem.

These findings are supported by several epidemiologic studies, including 1 small study that found a marginally significant reduction in cognitive decline among men who ate 1 fish meal per week.[26] In addition, the CHAP,[3] Rotterdam,[2] and Paquid[1] studies found statistically significant decreased risks of incident Alzheimer disease with higher fish consumption.

The evidence for association between the different types of ω-3 fatty acids and cognitive change was weak at best and only with α-linolenic acid in analyses restricted to long-term fish consumers. These findings are in contrast to our previous study, in which we observed strong reductions in Alzheimer disease risk among persons with high intakes of total ω-3 fatty acids, DHA, and α-linolenic acid. An explanation for the ω-3 fatty acids association with Alzheimer disease but not with cognitive decline is obscure at this point. We can only speculate that perhaps dietary ω-3 fatty acids have little impact on milder forms of cognitive decline. Another plausible explanation is that our measure of DHA and EPA intake is too imprecise to detect an association with cognitive change. One large population-based study examined the fatty acid composition of erythrocyte membranes in relation to 4-year change in Mini-Mental State Examination score and observed significant reductions in cognitive decline with increased levels of total ω-3 fatty acids, DHA, and EPA.[8]

We hypothesized that DHA would have the strongest association with cognitive change based on its abundance in brain tissue and evidence from animal models demonstrating superior learning and memory performance among DHA-fed rodents.[11,13,14,27-29] The absence of association with DHA raises the possibility that the observed fish association was due to some other dietary constituent or perhaps to another factor that is related to cognitive health and fish consumption. Overall fat composition is a likely dietary constituent underlying the association because adjustment for fat intake modified the fish association and was also independently associated with both cognitive decline[30] and Alzheimer disease.[31]

Confounding by related factors is another plausible explanation of the findings. Arguing against this explanation is that the fish consumers tended to have an unfavorable risk profile for cognitive change, including black race, lower alcohol consumption, and higher prevalence of cardiovascular conditions. Further, the association remained after adjustment for many healthy lifestyle behaviors and when persons with the lowest baseline cognitive scores were eliminated from the analyses.

A major strength of the CHAP study is the use of multiple cognitive tests and multiple periods of assessment that served to reduce bias and random error. The analytic method increased the ability to separate within-person cognitive change from between-person differences in cognitive ability.

This study suggests that eating 1 or more fish meals per week may protect against cognitive decline associated with older age. More precise studies of the different dietary constituents of fish should help to understand the nature of the association.

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